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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,642	12/22/2000	Thomas B. Albrecht	026.00041	4973

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EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/748,642	ALBRECHT ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/02/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 14-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/16/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: NCBI Taxonomy Browser

DETAILED ACTION

Status of Application/Amendment/Claims

1. Claims 6-8 and 14-16 are pending and currently under examination in this application. Claims 1-5, 19-13 and 17-18 were cancelled by Applicant in the communications filed 4/28/2003 and 12/18/2003.

2. Applicant's response filed 12/16/2004 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 09/23/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 12/16/04 was filed after the mailing date of the first action on the merits in this Application, under continued examination under 37 CFR 1.114, on 06/04/2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites, "wherein the viral replication is caused by a human cytomegalovirus." However, the metes and bounds of what is being claimed with this terminology is unclear and cannot be determined. In the instant case it is not clear what viral replication is caused by a cytomegalovirus? Does this claim language mean that the replication of any virus is caused by the replication of human cytomegalovirus, for example? Does this claim mean that the viral replication is the replication of human cytomegalovirus, for example? Does this claim mean that the viral replication, either cytomegalovirus or some other virus, is caused by some undisclosed property of human cytomegalovirus, for example? Therefore, claim 7 is indefinite. Claims 6 and 8 are rejected due to their dependence on a rejected claim.

Response to Arguments

6. Applicant's amendments to the claims, filed 02/02/2005, with respect to claims 7 and 15 have been fully considered. The rejection of claims 6-8 and 14-16 under 35 U.S.C. § 112, scope of enablement, has been withdrawn.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 6 and 7 (6-7 and 14-15) are rejected under 35 U.S.C. 102(e) as being anticipated by Potter et al. (U.S. Patent 6,015,787). The invention as set forth in claims 6-7 and 14-15 is drawn to a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of functional cellular protease in the cells or the subject by exposing the cells or administering to the subject a calpain inhibitor wherein the functional cellular protease is calpain.

Potter et al. disclose and claim a method of inhibiting calpain in a cell comprising administering a fusion protein of their invention that is a calpain inhibitor (claim 1) wherein the cell is an HIV infected cell (claim 8). Potter et al. disclose that "fusion proteins may be used to inhibit activation of NF-.kappa.B regulated viruses, e.g., cytomegalovirus, hepatitis B virus, herpes viruses, adenoviruses, HTLV-I, Sendai virus, human herpes virus 6, and HSV type 1 (see, e.g., Baeuerle, Biochem. Biophys. ACTA 1072:63-80, 1991)" (col. 12, lines 36-42). The disclosure of Potter et al., anticipates the instant invention as set forth in claims 6-7 and 14-15, because the patented claims of Potter et al. read on both in vitro and in vivo embodiments of inhibiting viral replication in a cell by inhibiting a functional cellular protease that is calpain and sets forth that cytomegalovirus is contemplated in the context of the invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 6-8 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (Reference 1 on PTO form 1449, filed July 19, 2002), Henkart et al. (reference 2 on PTO form 1449, filed July 19, 2002), Kido et al. (Reference 1 on PTO form 1449, filed December 16, 2004) and deJong et al. 1998 (Antiviral Research, Vol. 39: pp. 141-162).

Claims 6-8 and 14-16 are drawn to a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising

decreasing levels of functional cellular protease in the cells or the subject by exposing the cells or administering to the subject a calpain inhibitor that is E64d or Z-Leu-Leu-H.

Roizman et al. teach "A method for treatment of viral infections makes use of the target proteases disclosed herein which are vital to the viral life cycle" and that "The method of treatment disclosed herein is particularly applicable to the herpes virus simplex subtypes 1 or 2, but will be generally applicable to the herpes family, members of which are known to have extensive DNA homologies. Because of extensive sequence homologies to HSV-1 U.sub.L 26 in other organisms, e.g. cytomegalovirus (U.sub.L 80), Varicella-zoster virus (ORF33), Epstein-Barr virus, these treatment strategies are likely to be broadly applicable to all herpes virus (col. 9, lines 44-64). The state of the art recognizes that cytomegalovirus is a member of the herpes virus family (Entrez-PubMed Taxonomy Browser: subsection viruses, viewed 4/29/2005, printout attached).

Roizman et al. do not teach inhibition of the cellular protease, calpain with the specifically named calpain inhibitors, E64d or Z-Leu-Leu-H.

Henkart et al. teach methods wherein a calpain inhibitor is administered to virally infected cells (HIV), including wherein the calpain inhibitor is an E-64 derivative that is E64d (see for example column 3) and Z-Leu-Leu-H (see for example column 7). Henkart et al. disclose administering these inhibitors to an individual or ex vivo to cells of an individual for treatment of HIV infection. Henkart et al. teach that the calpain inhibitor of their invention may be used in conjunction with other treatments designed to inhibit viral replication in a host (col. 3, lines 52-54).

Kido et al. teach the extensive study of the proteolytic activation of animal enveloped viruses and that much is understood regarding the host cellular proteases that determine the pathogenicity and infectious tropism of viruses and that, "Intracellular and/or extracellular proteases are required for proteolytic activation of the viral envelope fusion glycoproteins and also for activation of cellular membrane fusion machinery (pg. 325, 1st paragraph). Kido et al. teach that, "The post-translational proteolytic cleavage of envelope glycoprotein precursors of enveloped viruses is essential for the infectivity and spread of the virus in the host organism since cleavage must precede the fusion process (pg. 328, Results and Discussion, 1st paragraph).

DeJong et al. teach that human cytomegalovirus is a major cause of morbidity in HIV infected individuals (pg. 153, col. 2, section 6.1) and that "Since the introduction of highly active antiretroviral treatment (HAART), i.e., combined therapy with potent HIV reverse transcriptase and protease inhibitors, two important changes in the occurrence of HIV associated CMV disease have been observed. On one hand, secondary to improved suppression of HIV replication and associated maintenance of a relatively intact immune system, the rate of CMV retinitis is declining substantially" (pg. 154, col. 1, 1st full paragraph). DeJong et al. teach that, "In conclusion, while advances in the treatment of CMV retinitis have been evident during the past decade, the development of treatment regimens with improved efficacy needs to continue to be pursued. Although the rate of CMV retinitis is declining in the HAART era, this decline should not lead to a relaxation of these efforts" (pg. 155, col. 1, 2nd full paragraph). DeJong et al. thereby teach the desirability of continuing the development of treatment regimens with

improved efficacy in order to treat HIV-infected, immunocompromised individuals that are at significant risk of CMV infection.

It would have been obvious to one of ordinary skill in the art to practice a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H, because methods of inhibiting herpes viral replication and treating herpes viral infections by inhibiting proteases vital to the herpes viral lifecycle were known in the art and generally applicable to other members of the herpes virus family, including cytomegalovirus (as taught by Roizman et al.), because cellular proteases were known to be proteases that were vital to the lifecycle of enveloped viruses (as taught by Kido et al.) and because cytomegalovirus is an enveloped virus, because the inhibition of the cellular protease, calpain, using E64d or Z-Leu-Leu-H in cells or subjects to provide a treatment for viral (HIV) infection was known in the art (as taught by Henkart et al.) and because these inhibitors could be used in conjunction with other treatments designed to inhibit viral replication in a host (as taught by Henkart et al.).

One of ordinary skill in the art would have been motivated to practice a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H in order to inhibit cellular proteases vital to the viral lifecycle so as to provide a treatment for viral infection, because CMV retinitis is associated with HIV infection and the need for developing treatment regimens

with improved efficacy was known in the art. Moreover, one of ordinary skill in the art would have been motivated to practice the method of the instant invention because the HAART treatment of HIV infection, as known in the art, employed a protease inhibitor in conjunction with other treatments designed to inhibit viral replication in a host and the calpain inhibitors E64d and Z-Leu-Leu-H were known in the prior art as cellular protease inhibitors that are usable in conjunction with other treatments designed to inhibit viral replication in a host.

One of ordinary skill in the art would have expected success in practicing a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H because protease inhibitors are known and used in the prior art in conjunction with other treatments designed to inhibit viral replication in a host (HAART) and because inhibition of a protease vital to the lifecycle of a herpes virus was known to be a successful for treating herpes virus infection and cytomegalovirus is a closely related DNA virus with extensive sequence homology.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 8 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henkart et al. and deJong et al., as applied above in view of Potter et al. (U.S. Patent

6,015,787). Claims 8 and 16, which depend from claims 7 and 14 respectively, recite the limitations wherein the calpain inhibitor is E64d or Z-leu-leu-H.

Henkart et al. teach methods wherein a calpain inhibitor is administered to virally infected cells (HIV), including wherein the calpain inhibitor is an E-64 derivative that is E64d (see for example column 3) and Z-Leu-Leu-H (see for example column 7). Henkart et al. disclose administering these inhibitors to an individual or ex vivo to cells of an individual for treatment of HIV infection. Henkart et al. teach that the calpain inhibitor of their invention may be used in conjunction with other treatments designed to inhibit viral replication in a host (col. 3, lines 52-54).

Henkart et al. do not teach that the calpain inhibitors E64d or Z-leu-leu-H are used to decrease cytomegalovirus replication.

DeJong et al. teach that human cytomegalovirus is a major cause of morbidity in HIV infected individuals (pg. 153, col. 2, section 6.1)

Potter et al. teach a method of inhibiting calpain in a cell comprising administering a fusion protein calpain inhibitor to an HIV infected cell (claims 1, 8) and that the fusion proteins of their invention can be used in the treatment of HIV-1 infection (col. 5, lines 59-67 bridge to col. 6, line 1). Potter et al. teach that the calpain inhibitors of their invention may be used to inhibit activation of NF-.kappa.B regulated viruses, e.g., cytomegalovirus, hepatitis B virus, herpes viruses, adenoviruses, HTLV-I, Sendai virus, human herpes virus 6, and HSV type 1 (see, e.g., Baeuerle, Biochem. Biophys. ACTA 1072:63-80, 1991)" (col. 12, lines 36-42).

It would have been obvious to one of ordinary skill in the art to practice a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H, because methods of decreasing cytomegalovirus by inhibiting calpain were known in the art (as taught by Potter et al.) and because E64d and Z-Leu-Leu-H were known and used in the art to inhibit calpain, thereby inhibiting viral replication (as taught by Henkart et al.).

One of ordinary skill in the art would have been motivated to practice a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H in order to decrease the replication (because inhibiting the activation of a virus is inherently inhibiting the replication of that virus) of NF-.kappa.B regulated viruses, including cytomegalovirus, so as to provide a treatment for viral infection because CMV is a major cause of morbidity in HIV infected individuals (as taught by deJong et al.).

One of ordinary skill in the art would have expected success in practicing a method of decreasing cytomegalovirus replication in cells or of treating cytomegalovirus infection in a subject comprising decreasing levels of the functional cellular protease, calpain, using the calpain inhibitors E64d or Z-Leu-Leu-H because these calpain inhibitors were known and used in the art to decrease viral replication by decreasing calpain activity (as taught by Henkart et al.) and because the inhibition of calpain is

taught in the art to inhibit the activation of cyclomegaloviruses (wherein activation of a virus inherently results in replication).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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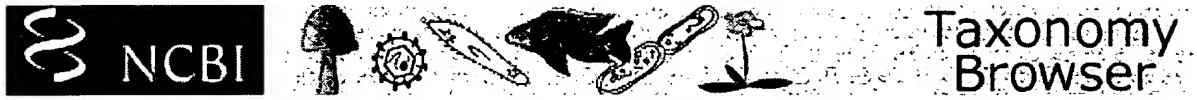

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Lineage (full): root; Viruses; dsDNA viruses, no RNA stage; Herpesviridae

ICTV homepage

- **Betaherpesvirinae** *Click on organism name to get more information.*
  - **Cytomegalovirus**
    - **Baboon cytomegalovirus**
      - **Baboon cytomegalovirus OCOM4-37**
    - **Cercopithecine herpesvirus 5**
    - **Cercopithecine herpesvirus 8** (Rhesus cytomegalovirus)
      - **Rhesus cytomegalovirus strain 68-1**
    - **Colobus badius cytomegalovirus 1**
    - **Colobus guereza cytomegalovirus 1**
    - **Human herpesvirus 5** (Human cytomegalovirus)
      - **Human herpesvirus 5 (strain 1042)**
      - **Human herpesvirus 5 (strain 119)**
      - **Human herpesvirus 5 (strain 2387)**
      - **Human herpesvirus 5 (strain 4654)**
      - **Human herpesvirus 5 (strain 5035)**
      - **Human herpesvirus 5 (strain 5040)**
      - **Human herpesvirus 5 (strain 5160)**
      - **Human herpesvirus 5 (strain 5508)**
      - **Human herpesvirus 5 strain AD169**
      - **Human herpesvirus 5 strain Eisenhardt**
      - **Human herpesvirus 5 strain Merlin**
      - **Human herpesvirus 5 strain PT**
      - **Human herpesvirus 5 strain Toledo**
      - **Human herpesvirus 5 strain Towne**
    - **Mandrillus cytomegalovirus**
    - **Phacochoerus africanus cytomegalovirus 1**
    - **Pongine herpesvirus 4** (Chimpanzee cytomegalovirus)
    - **Pongo pygmaeus cytomegalovirus 1**
    - **Porcine cytomegalovirus**
    - **Simian cytomegalovirus**
    - **Vervet cytomegalovirus CSG**
    - **unidentified cytomegalovirus**
  - **Muromegalovirus**
    - **Murid herpesvirus 1** (Murine cytomegalovirus)
      - **Murine cytomegalovirus (strain K181)**

- Murine cytomegalovirus (strain Smith)
- Murid herpesvirus 2 (Rat cytomegalovirus)
  - Rat cytomegalovirus Maastricht
- Roseolovirus
  - Human herpesvirus 6
  - Human herpesvirus 6A
    - Human herpesvirus 6 (strain GS)
    - Human herpesvirus 6 (strain Uganda-1102)
  - Human herpesvirus 6B
    - Human herpesvirus 6 strain Z29
  - Human herpesvirus 7
    - Human herpesvirus 7 (strain RK)
  - Pan troglodytes herpesvirus 6
- Tupaiid herpesvirus 1
- Tupaiid herpesvirus 2
- unclassified Betaherpesvirinae
  - Aotine herpesvirus 1
  - Atypical cytopathic virus
  - Elephant herpesvirus 1
  - Macaca mulatta cytomegalovirus
  - Mandrillus herpesvirus beta
  - Porcine cytomegalovirus B6
  - Porcine cytomegalovirus OF-1
